

# Best Practice

## EVIDENCE-BASED CASE REVIEW

### Should we look further for cancer in a patient with venous thromboembolism?

#### Objectives

- To show how disease probability can be used to guide clinical decisions
- To learn what proportion of patients with venous thromboembolism will have occult cancer at presentation and in what proportion cancer will develop
- To learn which types of cancer are commonly found in patients with venous thromboembolism

A 71-year-old woman with venous thromboembolism was referred to us to determine whether a workup for cancer was indicated. She had been hospitalized because of deep venous thrombosis of her left leg and pulmonary embolism; she had no history of venous thromboembolism or cancer. For the past few months, she had the feeling of being “full” before she had eaten much but had no other constitutional or gastrointestinal symptoms. On physical examination, she was found to be obese (body mass index<sup>\*</sup>=33), and there was fibrocystic nodularity in both breasts. She also had a trace of symmetric edema in her ankles. Laboratory test values showed mild normocytic anemia, but routine chemistry test results were normal, as were those of her liver function tests, urinalysis, activated protein C resistance, proteins C and S and antithrombin III concentrations, antiphospholipid antibody, and a chest film.

#### OUR QUESTIONS

We quickly developed 2 questions that we hoped to answer before advising about the patient’s care. Of patients with venous thromboembolism without a history of cancer, what proportion have occult cancer that could be detected either at the time the venous thromboembolism was diagnosed or in a short follow-up period? In these same patients, what types of cancer are found?

\*The body mass index is calculated as weight in kilograms divided by the square of the height in meters: weight (kg)/[height (m)]<sup>2</sup>.

#### SEARCHING FOR EVIDENCE

We searched MEDLINE from 1966 through August 17, 1998, using the following search items: pulmonary embolism, thromboembolism, thrombophlebitis, venous thrombosis, deep venous, venous thromboembolism, trousseau, neoplasms, occult neoplasms, occult cancer, occult malignancy, and paraneoplastic syndromes. This search strategy identified 494 articles. We reviewed these articles first by title and then by abstract, yielding 5 reviews, 22 original articles, and one letter.<sup>6-28</sup>

#### APPRAISING THE EVIDENCE

Of the 5 review articles identified, 2 were traditional reviews without reference to how their data were located or validated.<sup>1,2</sup> The 2 meta-analyses used trials that included patients who were known to have cancer at the time they were diagnosed with venous thromboembolism.<sup>3,4</sup> This would be expected to result in an overestimation of the incidence of occult cancer in patients with venous thromboembolism. Thus, we were unable to use their data to answer our questions. The decision analysis was designed to assess the effectiveness and cost-effectiveness of strategies for investigating patients for a diagnosis of cancer, and these were not our questions.<sup>5</sup>

We then appraised the 23 original cohort studies, using the criteria shown in table 1. The methods of these studies varied considerably. Only 7 studies met enough criteria to be included in our final analysis.<sup>6-12</sup> Of these, 3 studies did not use a standardized diagnostic workup to test for occult cancer,<sup>6,8,10</sup> and 2 studies did not consistently ap-

Table 1

#### Validity criteria

- Excluded known cancer at the time venous thromboembolism was diagnosed
- Objective diagnostic criteria used to document venous thromboembolism
- Consistent diagnostic workup used to screen for cancer
- Objective diagnostic criteria used to document cancer
- Follow-up was for at least 1 year
- Cohort selection appeared free from bias

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## Summary points

- Based on the research evidence we found, the incidence of detectable malignancy at the time of a diagnosis of venous thromboembolism is between 1.9% and 7.5%
- We estimated our threshold for testing for occult cancer in this patient to lie between 2% and 4%; therefore, we suggested selected testing
- The types of cancer most commonly found in patients with venous thromboembolism were colon, prostate, lung, hematologic, breast, ovarian, skin, and liver
- After selected testing failed to identify occult cancer, our patient's probability of occult cancer was now below our threshold for further undirected testing

ply their diagnostic workup to all patients.<sup>11,12</sup> Only 3 studies reported objective diagnostic criteria for documenting cancer.<sup>6,9,10</sup>

## SUMMARIZING THE EVIDENCE

The data from the 7 studies we selected are presented in table 2.<sup>6-12</sup> The patient populations were similar, with mean ages between 56 and 65 years, and 44% to 55% were women. The settings were all tertiary referral centers.

In 4 studies, cohorts were divided into patients with idiopathic and those with secondary causes of venous thromboembolism<sup>7,9,11,12</sup>; however, each of these defined secondary venous thromboembolism differently. Because this made comparisons difficult, we combined all patients with idiopathic and secondary venous thromboembolism for our analysis.

These data suggest that the incidence of detectable malignancy at the time of a diagnosis of venous thromboembolism is between 1.9% and 7.5%. Thus, if we assume that no cancer would be detected without an evaluation by a physician, between 13 and 50 patients with venous thromboembolism would have to be evaluated for 1 case of occult malignancy to be detected. The incidence of malignancy being detected during follow-up for venous thromboembolism is between 1.2% and 17.8%. Thus, between 6 and 83 patients with venous thromboembolism would need to be evaluated for 1 case of malignancy to be detected in follow-up. The heterogeneity of the reported incidence is likely due to variations in the diagnostic strategy used to detect occult cancer and differences in length of follow-up. For example, Bastounis and co-workers<sup>11</sup> report a higher incidence of cancer at the time of a diagnosis of venous thromboembolism than did Prandoni and colleagues.<sup>9</sup> However, Bastounis and associates used a

Table 2 Studies that met validity criteria

Study and year	Design	Patients with cancer found after a diagnosis* of venous thromboembolism, No. (%)	Patients with cancer found in follow-up after a diagnosis of venous thromboembolism,† No. (%)	Mean length of follow-up, mo	Diagnostic strategy used
Gore et al, 1982 <sup>6</sup>	Retrospective	4/88 (4.5)	15/84 (17.9)	ca 24‡	Not standardized
Aderka et al, 1986 <sup>7</sup>	Prospective	NA	14/83 (16.9)	42	ESR, CBC, smear, chemistry panel, fibrinogen, prothrombin time, chest x-ray, and stool occult blood
Goldberg et al, 1987 <sup>8</sup>	Retrospective	NA	22/370 (5.9)	30	Not standardized
Prandoni et al, 1992 <sup>9</sup>	Prospective	5/260 (1.9)	13/250 (5.2)	80	ESR, CBC, chemistry panel, liver function tests, urinalysis, and chest x-ray
Nordstrom et al, 1994 <sup>10</sup>	Retrospective	NA	150/1,383 (10.8)§	ca 42‡	Not standardized
Bastounis et al, 1996 <sup>11</sup>	Prospective	22/293 (7.5)	7/264 (2.6)	24	CBC, ESR, chemistry panel, liver function tests, serum protein electrophoresis, urinalysis, CEA, and chest x-ray with or without abdominal CT scan
Monreal et al, 1997 <sup>12</sup>	Retrospective	26/685 (3.8)	8/659 (1.2)	16	ESR, CBC, smear, liver function tests, serum protein electrophoresis, lactate dehydrogenase, CEA, prostate specific antigen, chest x-ray, abdominal CT scan or abdominal sonogram

ca = circa; NA = data not available; CT = computed tomography; ESR = erythrocyte sedimentation rate; CBC = complete blood count; CEA = carcinoembryonic antigen.

\*Included only patients with cancer found at the time venous thromboembolism was diagnosed or within first month after idiopathic or secondary venous thromboembolism.

†Includes only patients with cancer diagnosed at least 1 mo after idiopathic or secondary venous thromboembolism.

‡Studies did not report mean length of follow-up.

§Study may include patients with cancer diagnosed within first month after venous thromboembolism.

more extensive diagnostic strategy, which may have detected more cases of occult malignant neoplasm. In addition, the studies that report longer follow-up periods also report a higher incidence of cancer in follow-up after a diagnosis of venous thromboembolism. The correlation between venous thromboembolism and cancer may be called into question at these longer periods of follow-up, however.

The types of cancer found in the 7 studies and their proportion are presented in table 3.<sup>6-12</sup>

### USING THE EVIDENCE

In the absence of research evidence and of a formal threshold analysis, we could not confidently place our threshold for testing on the probability scale. Nonetheless, we estimated it to be between 2.0% and 4.0%; above this figure, we would search for selected causes. We reasoned our threshold should be as low as 2.0%, given how serious and how potentially treatable some of these cancers are. We were surprised to learn that our patient had between a 1.9% and 7.5% probability of having detectable occult malignancy. This incidence of cancer fell above our threshold for testing; thus, we recommended selected testing. Based on the data on the types of cancer found in this patient population, we expected the most common cancers to be detected using screening techniques that were appropriate to this patient's age.

The patient underwent a breast examination by a physician, pelvic examination, cervical smear, mammography, and flexible sigmoidoscopy. The

results of these tests did not suggest evidence of malignancy. A complete blood count was repeated, and the mild normocytic anemia had resolved. Because our patient had early satiety, we recommended an upper endoscopy; however, she elected to undergo a barium upper gastrointestinal series, the results of which were normal.

The normal results of these tests served to further lower the patient's probability of having occult malignancy, and it was now below our threshold for further undirected testing. We discussed this with the referring physician and the patient, and they agreed.

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Table 3 Incidence of cancer by site

Site	Total no.	(%) of patients
Colon-rectum	44	(15)
Prostate	38	(13)
Lung	30	(10)
Hematologic	18	(6)
Breast	17	(6)
Ovarian	14	(5)
Skin	12	(4)
Liver	10	(4)
Miscellaneous	103	(36)
Total	286	(99)

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### A Book To Make You Think

*Assuming the Risk: The Mavericks, the Lawyers, and the Whistleblowers Who Beat Big Tobacco* by Michael Orey, Little Brown, 1999, \$24.95

While the US tobacco industry settled the mammoth tobacco suits lodged by the 50 US states, elsewhere in the world the tobacco giants continue their denials and questionable marketing practices seemingly oblivious. From this perspective, the events described in Michael Orey's book seem more like a minor skirmish on the edge of the tobacco control movement than a victory for the combined forces of governments and the public health community. Keeping in mind this minor quibble, *Assuming the Risk* is a tremendously readable and interesting book. Like the fictional novels of John Grisham, it is the characters who drive much of the book's plot.

As with most events that change the course of a movement, the US Master Settlement Agreement truly began years earlier in a small and poor county of the poorest state in the United States. Thus, starting with the Willie Horton case, which would serve as the linchpin and common reference point for the proceedings that followed, readers are led through the many cases and events that would culminate, years later, with Mississippi's decision to file suit against the US tobacco industry, a move subsequently followed, probably most notably by Minnesota, by the remaining 49 states. As Orey proceeds with his discussion, readers are introduced to a growing cast of characters, their every personality quirk and foible apparently disclosed by the author. Thus we are told of Merrill Williams' quasi-neurotic tantrums, Jeffery Wigand's difficult temperament, and Mike Moore's career-long determination to do good, as well as many other thumbnail portraits.

Where Orey leaves readers wanting is in not discussing the merits of the US states' litigation-driven strategy. Is the \$246 billion Master Settlement Agreement really a victory for public health? People are now questioning whether any deal made with the tobacco industry can ever be consistent with the interests of public health. While discussing the role of Congress in legislating the first multi-state agreement, Orey never addresses the apparent lack of coherence exhibited by US politicians on the issue of tobacco control. After reading this book, you get the feeling that the US public and politicians feel that no further legislative or regulatory action is necessary now that the tobacco industry has been forced to pay.

Perhaps one cannot fault Orey for sticking to what he does best, which is describing the situations, the people, and the maneuvering that lead to US tobacco's first major setback. Written in a journalistic style that eschews legal jargon in favor of plain language, this book will be of most interest to those outside the legal profession. If not a must read, at least a good read.

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### On the Cover

The photograph on the cover of this issue of *wjm* is the work of Douglas S Diekema. Dr Diekema is a pediatric emergency medicine physician and director of medical ethics at Children's Hospital and Regional Medical Center in Seattle, Washington. When not caring for patients or teaching at the University of Washington School of Medicine, he enjoys photography and hiking.